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VIEWPOINT

# The pruritogenic role of the type 2 immune response in diseases associated with chronic itch

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## Abstract

While there is a vast array of aetiologies that may lead to chronic pruritus, recent data suggests that many of these conditions share similar interactions between keratinocytes, nerves, and the immune system. Specifically, the type 2 immune response, including Th2 T Cells and their related cytokines, has been noted to play a major role in the development of pruritus in a variety of itchy conditions. To date, atopic dermatitis is the most striking example of this pathogenesis. However, the body of literature supporting its role in many other itchy conditions, including other inflammatory, bullous, as well as systemic diseases, continues to grow. In addition, new treatments targeting this type 2 immune system continue to be developed and investigated. In the current review, we present the current body of literature supporting the role of the type 2 immune response in itchy conditions beyond atopic dermatitis as well as potential therapeutic options that target this pathway for chronic itch.

**KEYWORDS**
biomarkers, cytokines, inflammation, itch, T cells

## 1 | INTRODUCTION

Chronic pruritus (CP) is defined as itch that lasts longer than 6 weeks and can be a manifesting symptom of many dermatologic, systemic and neuropathic diseases.[1] While the mechanistic aetiologies of the extensive list of pruritus-causing conditions all differ, a vast majority of these conditions share a similar "cross-talk" between keratinocytes, nerves and the immune system that induces itch.[2] The type 2 immune response, including Th2 cells and related cytokines, is one part of the immune response that seems to be heavily involved in the development of pruritus in many of these conditions.

Th2-related cytokines include IL-4, IL-13, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP). All of these cytokines have previously been reported in atopic itch, and Figure 1 depicts their general mechanism in chronic itch.[3–11] In addition, periostin, an extracellular matrix protein, is highly associated with amplifying the type 2 immune response. Periostin is generated by epidermal keratinocytes under stimulation of TSLP and by dermal fibroblasts under stimulation of IL-4 and IL-13.[12,13] Recently, periostin was found to directly stimulate sensory nerve fibres and causes pruritus by binding to Alpha-V-Integrin receptors located on their surface.[13] Moreover, periostin causes a positive feedback loop of chronic pruritus and type 2 inflammation by promoting release of TSLP from epidermal keratinocytes, and release of IL-31 from dermal macrophages, basophils and eosinophils.[12,14]

The role of the type 2 immune response in inducing itch has already been well established in atopic dermatitis and is the most prominent example to date of Th2-driven pruritus.[2] IL-4 and IL-13 expressions have been shown to be increased in lesional skin of AD patients.[15] Additionally, IL-31, coined as the "itchy cytokine" plays a role in the pathogenesis, pruritus and peripheral nerve sensitization seen in AD by binding to the IL-31-Receptor-Alpha

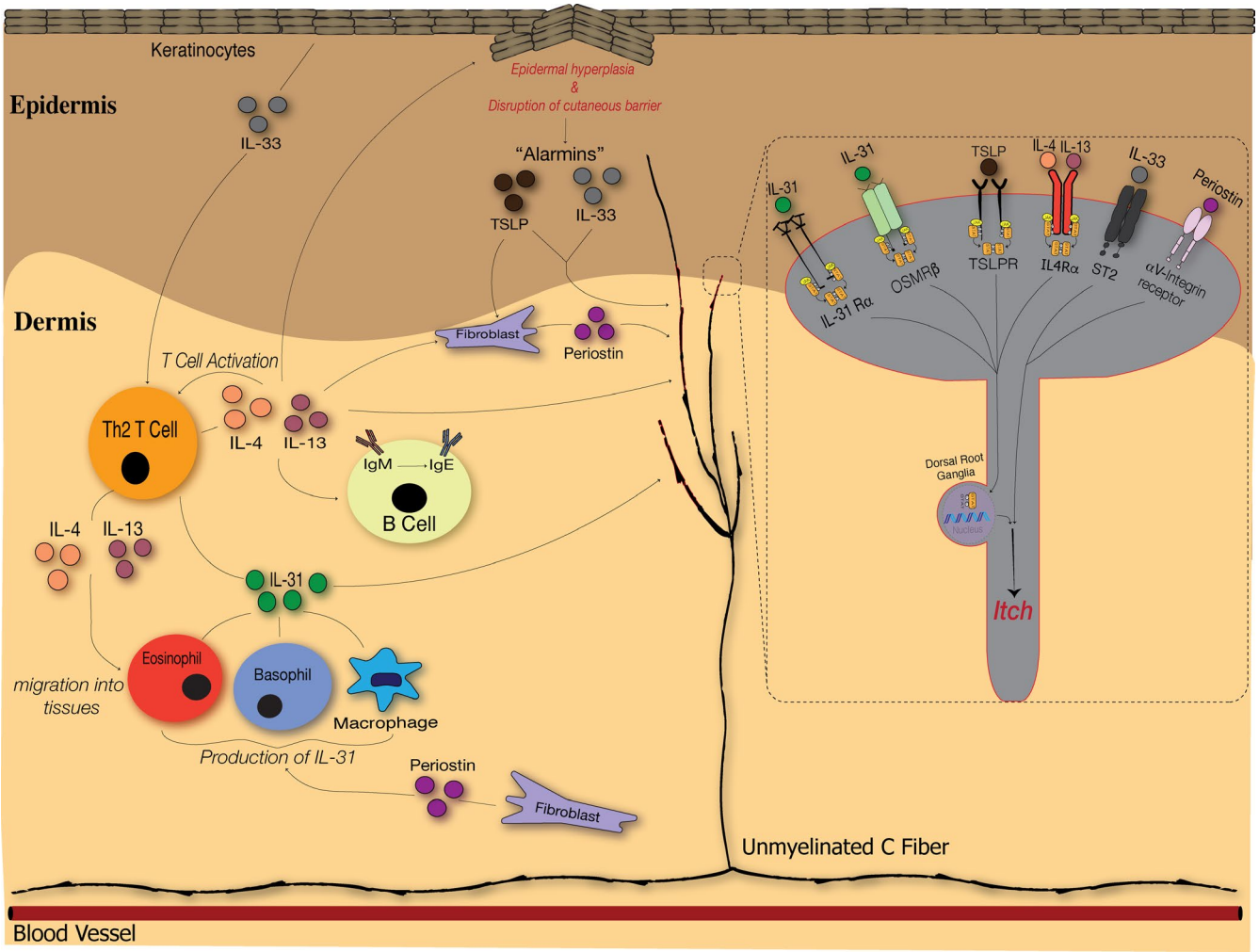


**FIGURE 1** Activated Th2 T Cells release IL-4 and IL-13, which bind to the IL-4 receptor subunit α (IL-4Rα) receptor leading to sensitization and direct stimulation of sensory neurons, proliferation of Th2 cells, migration of lymphocytes to tissues, survival of B cells and class switching to IgE, disruption of the cutaneous barrier and epidermal hyperplasia. Activated Th2 cells, macrophages, basophils and eosinophils release IL-31, which induces pruritus by binding to the IL-31-Receptor-Alpha (IL-31Rα) and Oncostatin M Receptor-Beta (OSMRβ) located on keratinocytes, dermal immune cells and sensory neurons within the epidermis and dermis. Epidermal keratinocytes release "alarmins", which are epithelial derived cytokines that trigger a Th2 immune response and include TSLP and IL-33. TSLP causes pruritus by binding to the Thymic Stromal Lymphopoietin Receptor (TSLPR) located on sensory neurons. IL-33 binds to the ST2 receptor and causes release of IL-13 from Th2 cells, direct stimulation of sensory neurons, and also plays a role in lymphocyte chemotaxis to affected areas. Interestingly, the IL-4Rα, IL-31Rα, OSMRβ and TSLPR are all associated with the Janus Kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) pathway of intracellular signalling

(IL-31Ra) and Oncostatin M Receptor-Beta (OSMRb) located on keratinocytes, dermal immune cells, and sensory neurons within the epidermis and dermis.[7,16,17] However, the literature supporting the type 2 immune response's involvement in other pruritic conditions has been not well addressed, but nonetheless important. Table 1 summarizes skin diseases and chronic itch conditions where Th2-related cytokines are involved in itch. In this viewpoint article, we aim to outline the role of type 2 immune response in many non-atopic dermatitis pruritic conditions and argue on the important role of type 2 inflammation in chronic itch. We also aim to present the rationale for using biological treatments that effectively reduce chronic itch by targeting specific components of the type 2 immune response.

## 2 | THE ROLE OF THE TH2 IMMUNE RESPONSE IN CHRONIC PRURITIC CONDITIONS

### 2.1 | Prurigo nodularis

Prurigo nodularis (PN) is a chronic pruritic skin condition characterized by severely pruritic nodules with an incompletely understood pathophysiology likely caused by a complex interplay of aberrant signalling between IL-4, IL-13, IL-31, TSLP and periostin.[18] Studies have reported that type 2 cytokines play a key role in the pathogenesis of PN.[19] PN is also reported to have a 50-fold increase of IL-31 mRNA in lesional skin.[20] We recently reported an increased amount of

**TABLE 1** Type 2 cytokines play a crucial role in the production of pruritus in many dermatologic conditions

| Cytokines | Binds to | Released by | Implicated diseases | References |
|---|---|---|---|---|
| IL-4 | IL-4a on keratinocytes, sensory neurons, and dermal immune cells | Th2 cells | AD, PN, CSU, SSc, DM, CTCL | 3–6,15,18,26,30,43,48,52 |
| IL-13 | IL-4Ra on keratinocytes, sensory neurons, and dermal immune cells | Th2 cells | AD, PN, BP, CSU, SSc, CTCL, CKD-aP | 10,15,18,30,43,52,59 |
| IL-31 | IL-31Ra, and OSMRb on keratinocytes, dermal immune cells, and sensory neurons | Th2 cells, macrophages, basophils, and eosinophils | AD, PN, BP, CSU, SD, SC, SSc, DM, CTCL, CKD-aP, CPUO | 7,12,14,16–18,20,21,24,29,30,33–35,44,48,52–54,58,65 |
| IL-33 | ST2 Receptor on sensory neurons, and dermal immune cells | Epidermal keratinocytes | AD | 8,10,12 |
| TSLP | TSLP-R on sensory neurons and keratinocytes | Epidermal keratinocytes | AD, PN, CSU, SC | 8,9,18,34 |
| Periostin | Alpha-V-Integrin receptors on sensory neurons, fibroblasts, and dermal immune cells | Keratinocytes, macrophages, and fibroblasts | AD, PN, BP, SD, SC | 12,13,18,22,34,35 |

Abbreviations: AD, Atopic dermatitis; BP, Bullous pemphigoid; CKD-aP, Chronic kidney disease-associated pruritus; CPUO, Chronic pruritus of unknown origin; CSU, Chronic spontaneous urticaria; CTCL, Cutaneous T-cell lymphoma; DM, Dermatomyositis; OSMRb, Oncostatin M Receptor Beta; PN, Prurigo nodularis; SC, Scabies; SD, Stasis dermatitis; SSc, Systemic sclerosis; TSLP, Thymic Stromal Lymphopoietin.

dermal IL-31 (+) cells, IL-31Rα (+) cells and epidermal IL-31Rα expression in lesional PN skin compared to healthy controls that were significantly correlated with itch intensity.[21] Moreover, we found that dermal deposition of periostin is increased in PN lesions compared to healthy controls and is significantly associated with both itch intensity and the amount of dermal IL-31Ra (+) cells.[22] Altogether, Th2 related immune cells and cytokines likely play a prominent role in both the pathogenesis and pruritus associated with PN.

## 2.2 | Bullous pemphigoid

Bullous Pemphigoid (BP) is the most common type of autoimmune subepidermal blistering disease that often involves severe CP as a presenting symptom that may precede the development of blisters.[23] A recent study found increased levels of dermal IL-31 (+) cells, dermal OSMRb (+) cells, epidermal and dermal IL-31Ra expression, dermal IL-13 (+) cells and dermal deposition of periostin in active BP blistering lesions compared to healthy controls that are all significantly associated with itch severity.[12] While the majority of dermal IL-31 (+) cells were eosinophils, this study also found increased amounts of dermal basophils in active BP lesions that were significantly associated with pruritus. This is likely due to IL-31 acting as a chemoattractive agent for both eosinophils and basophils in active BP lesions.[24] Altogether, the significant association of cells associated with key components of the Th2 immune response with the itch severity in BP likely points to a dual role of both disease pathogenesis and disease-associated pruritus that the Th2 immune response plays in BP.

## 2.3 | Chronic spontaneous urticaria

Chronic Spontaneous Urticaria (CSU) presents with CP as a common disease feature and is characterized by recurrent wheals, angioedema or both over a period of more than 6 weeks without a specific trigger.[25] Ferrer et al. first reported increased IL-4 serum levels in CSU patients compared to healthy controls.[26] Later studies have found increased levels of IL-13, IL-31, IL-33 and TSLP serum levels in CSU patients compared to healthy controls.[27–29] Moreover, there are significantly higher serum levels of IL-31 in CSU patients with the most severe pruritus compared to milder forms of CSU, supporting the notion that IL-31 contributes to CSU-associated itch more than other aspects of disease activity.[29] Basophils expressing both the IL-31Ra and the OSMRb are increased in lesional skin of CSU and are likely the main cellular sources of the elevated IL-4, IL-13 and IL-31 in CSU.[30] Moreover, another study found IL-31 levels were significantly higher in CSU patients with ANA titre >1:160 compared with those who were negative for ANA or with titres of 1:80.[31] On the whole, recent findings point to a major role of the type 2 immune response in both the pathogenesis and the pruritus of CSU, although the complete understanding of these disease entities has yet to be fully elucidated.

## 2.4 | Stasis dermatitis

Stasis dermatitis (SD) is caused by chronic venous insufficiency and was the most commonly reported dermatosis to cause the complaint of itch in a cohort of elderly patients with CP.[32] In SD, the extravasation and cellular accumulation of hemosiderin can cause skewing of local macrophages towards the M2 phenotype (CD163+), which are closely associated with the Th2 immune response as they can be activated by IL-4 and IL-13 and are capable of producing IL-31.[33] A recent study found an increase in the number of M2 macrophages within the lesional skin of SD patients was significantly associated with the presence of severe pruritus.[34] Moreover, this study found increased amounts of dermal periostin, Th2 T cells, basophils, and IL-31 within lesional SD skin. In a murine model, TSLP and periostin were shown to have the ability to skew macrophages toward an M2 phenotype and stimulate IL-31 production.[35] Altogether, SD-associated CP is likely due to an interplay of the cells and cytokines involved in the Th2 immune response stimulating lesional M2 macrophages to release IL-31 and induce pruritus.

## 2.5 | Scabies

Scabies is a common contagious skin disease caused by an infestation of the skin by *Sarcoptes Scabiei var. hominis*.[36] Severe persistent pruritus is a hallmark symptom of ordinary scabies.[37] Compared to healthy skin and tick bite lesions, a recent study found a significant increase of IL-31 in scabies lesions that is predominantly produced by dermal IL-31 (+) M2 macrophages.[35] This study also found a statistically significant increase of dermal C–C chemokine receptor type 4 (CCR4+) Th2 T cells, eosinophils, basophils, periostin and epidermal TSLP within scabies lesions compared to normal skin and tick bites. Lastly, a ligand for CCR4+ Th2 T cells, Thymus and Activation-Regulated Chemokine (TARC), was increased in scabies lesions compared to healthy skin. A later case report found TARC levels significantly decreased following successful treatment of active scabies.[38] The mechanism of scabies-associated pruritus is not yet fully understood but recent studies point toward a prominent role of a Th2-mediated process.

## 2.6 | Systemic sclerosis

Systemic Sclerosis (SSc) is an autoimmune connective tissue disorder characterized by abnormal fibrotic processes and excessive collagen production resulting in fibrosis of the skin and internal organs.[39] The prevalence of CP in SSc is reported to be 43–62% with a profound impact on quality of life.[40–42] SSc-associated pruritus is likely due to a combination of sensory nerve fibre entrapment from collagen deposition as well as direct stimulation of nerve fibres by the same Th2 mediated immune processes that drives the disease. Specifically, serum levels of IL-4 and IL-13 are elevated in patients with SSc.[43] These cytokines play a role in activating dermal fibroblasts to produce collagen as well as inducing local macrophages to become M2 macrophages, which are also elevated in SSc patients compared to healthy controls.[43] A study found serum levels of IL-31 were significantly elevated in SSc patients compared to healthy controls. Moreover, increased levels of IL-31 within the raised blister fluid of active lesions were characteristic of a subgroup of SSc patients with severe pruritus compared to SSc patients without pruritus.[44] Altogether, IL-4 and IL-13 likely drive SSc-associated pruritus in an indirect manner by activating fibroblasts and M2 macrophages, while the significant association of IL-31 with the severity of pruritus may point to a more direct role in SSc-associated pruritus.

## 2.7 | Dermatomyositis

Dermatomyositis (DM) is an idiopathic inflammatory myopathy thought to be autoimmune in nature.[39] Pruritus is a common cutaneous manifestation of DM, and one observational study of 70 DM patients found the mean severity of their pruritus to be moderate VAS of 5.4 (Visual Analog Score from 0–10).[45] While the pathogenesis of DM is not completely understood, two studies suggest an increase in Th2-related cells compared to Th1-related cells in the peripheral blood of DM patients.[46,47] In a novel study on DM-associated pruritus, Kim et al. enrolled 191 DM patients and found >90% of patients experienced pruritus.[48] They also found levels of IL-31 and IL-31Ra in lesional skin of DM patients was significantly higher than healthy controls and positively correlated with VAS itch scores. Flow cytometry showed that CD4+ Th2 T cells were significantly elevated in DM lesions and were the predominant cell type responsible for IL-31 production. IL-4 expression was significantly upregulated in lesional DM skin but was not correlated with VAS itch scores. Finally, they demonstrated lenabusum, a nonpsychoactive cannabinoid derivative, significantly downregulated IL-4 and IL-31 in CpG stimulated peripheral blood mononuclear cells that were collected from DM patients in the study.[48] A recent phase II clinical trial of lenabusum in DM patients with refractory skin disease has shown clinically significant improvement in DM disease severity scores, cutaneous photosensitivity, pruritus, fatigue and sleep.[49] As a whole, given the high prevalence of pruritus in DM along with the significant association between the VAS itch scores with IL-31 and its respected receptors, DM-associated pruritus is likely in part driven by key cells and cytokines of Th2 immune response.

## 2.8 | Cutaneous T-cell lymphoma

Cutaneous T-cell lymphomas (CTCL) are a group of primary non-Hodgkins T-cell lymphomas characterized by infiltration of malignant T cells into the skin.[50] A large retrospective analysis revealed 62% of early-stage CTCL patients experienced pruritus with a mean pruritus VAS of 3.4, while 83% of late-stage CTCL patients experienced pruritus with a mean pruritus VAS of 6.6.[51] The

pathophysiology of CTCL is hypothesized to evolve from an early-stage Th1-mediated disease to a late-stage Th2-mediated disease as evidenced by increasing serum levels of IL-4, IL-13, IL-31, CCR4 (+) Th2 T cells, IgE and Eosinophils as the disease progresses.[52] Singer et al. first-reported serum levels of IL-31 were significantly correlated with CTCL-associated pruritus.[53] Nattkamper et al. later found increased expression of epidermal and dermal IL-31, IL-31Ra, and OSMRb within CTCL lesional skin compared to healthy controls, and they were significantly correlated with VAS of pruritus severity.[54] Altogether, the increased prevalence and severity of pruritus in late-stage CTCL along with the increased serum levels of Th2 related cells and cytokines points to a significant relationship of the Th2 immune response in CTCL-associated pruritus.

### 2.9 | Chronic kidney disease-associated pruritus

Chronic kidney disease-associated pruritus (CKD-aP), is defined as the itching directly related to end-stage kidney disease and has an estimated current prevalence of 55% amongst adult dialysis patients.[55,56] The aetiology of CKD-aP is not well understood and is likely multifactorial. Recent research suggests the potential role of type 2 immune pathway of this itch.[57] Ko et al. found serum levels of IL-31 were significantly higher in dialysis patients with pruritus compared to dialysis patients without pruritus; moreover, this study demonstrated a positive exposure-response relationship between serum levels of IL-31 and VAS of pruritus intensity.[58] A later study by Oweis et al. found dialysis patients had significantly elevated serum levels of IL-31 compared to healthy controls, although IL-31 was not significantly related to VAS itch intensity.[59] However, this study found a significant relationship of IL-13 with VAS itch severity. There is no established gold standard of treatment for CKD-aP, and the definitive treatment is a kidney transplant. While a recent case report showed treatment with dupilumab resulted in significant improvement of severe refractory CKD-aP in a post-renal transplant patient, more studies are needed to confirm this case and determine the overall efficacy of attenuating the Th2 immune response to treat CKD-aP.[60] Therefore, the aetiology of CKD-aP is likely multifactorial, but the Th2 immune response plays a role that should be further investigated.

### 2.10 | Chronic pruritus of the elderly and chronic pruritus of unknown origin

Chronic Pruritus of the elderly is defined as CP experienced by people 65-year old and above.[61] There is a significant overlap of chronic itch in the elderly and Chronic Pruritus of Unknown Origin (CPUO) as both conditions have an unknown aetiology of pruritus and are associated with immune dysregulation.[62] Transformation of the immune system during the process of ageing, known as immunosenescence, is hallmarked by a progressive decline of the Th1 immune response with a simultaneous increase in Th2 immune activity.[63] This overactive Th2 immune response, particularly via IL-4 and IL-13, may in part be responsible for the cutaneous barrier disruption that occurs with ageing and may also predispose elderly patients to develop chronic itch.[64] A recent study found serum levels of IL-31 were significantly increased in patients with CPUO compared to healthy controls, concluding the presence of CPUO was significantly and independently associated with higher levels of IL-31.[65] Additionally, a recent histopathological retrospective analysis demonstrated patients with CPUO were found to have a significantly elevated amount of dermal Th2 T cells and a significantly decreased amount of dermal Th1 T cells compared to healthy controls.[66] Together, elderly patients with CP and patients with CPUO exhibit elevated IgE, peripheral eosinophilia, decreased dermal Langerhans cells and CD8 lymphopenia compared to age-matched healthy controls, pointing to the role of systemic Th2 immune activation in both diseases.[63]

## 3 | TH2-TARGETED TREATMENTS FOR CHRONIC PRURITUS

### 3.1 | Dupilumab

Several of the biologic drugs that reduce Th2 type immunity have significant anti-pruritic effects. Dupilumab, an anti- IL-4Rα monoclonal antibody, can rapidly improve pruritus in AD, CP of the elderly, CPUO, PN, BP, CSU and CTCL.[67] For AD, combined data from phase III clinical trials of dupilumab included 1,379 patients and found at least a 4-point improvement of peak pruritus Numerical Rating Scores (NRS) in 48% treated every 2 weeks, in 50.3% of patients treated every week, and in 15% of patients treated with placebo by week 16 of treatment.[68,69] In particular, dupilumab represents a promising treatment for elderly patients with AD, as a recent retrospective analysis of 276 elderly patients with AD found treatment with dupilumab for 16 weeks to be efficacious and safe in this challenging patient population.[70] Moreover, another recent case series reported dupilumab successfully treated CP of the elderly as well as Chronic Eczematous Eruption of Aging (CEAA), a condition in which the ageing immune system undergoes a switch to Th2 predominant response that drives the eruption and pruritus.[61,71] A recent retrospective case series of 15 CPUO patients who reported a peak pruritus NRS of 8 or higher found all patients responded with their collective median peak pruritus NRS decreasing from 8 to 1 after treatment with dupilumab.[72] For PN, a recent retrospective study of 27 patients found a significant reduction of peak pruritus NRS from an average baseline of 8.9 down to 6.3 by week 4 and to 2.7 by week 16 of treatment with dupilumab.[73] These findings are congruent with an earlier retrospective cohort of 16 PN patients treated with dupilumab that found complete resolution in 31% of the patients, partial resolution in 56% of the patients, and a decrease of peak pruritus NRS from a baseline average of 8 to 3 after 3 months of treatment.[74] For BP, two case reports

have found off-label use of dupilumab effectively improved self-reported pruritus after weeks of treatment with complete resolution of the blisters after months of treatment.[75,76] A recent case series of dupilumab for 13 patients with BP found 53.8% of patients achieved both self-reported improvement in pruritus as well as disease clearance with an additional 34% of patients reporting at least satisfactory control of their pruritus.[77] Given the preliminary success of dupilumab for PN and BP to date, there is an expanded use of accesses of dupilumab allowed for these diseases in addition to ongoing phase III clinical trials of dupilumab for patients with these diseases as well.[78–80] For CSU, a case series of six patients with both CSU and AD that were treated with dupilumab found all of the patients had a significant reduction in their Urticarial Activity Score (UAS) from a baseline of 30 or more to 3 or less; however, direct reduction in pruritus was not recorded in this study.[81] Given these findings, there are currently ongoing phase 2 and phase 3 studies of dupilumab for patients with CSU.[82,83] Finally, a recent case report of a patient with Sezary Syndrome, a common variant of CTCL, reported successful reduction in baseline peak pruritus NRS of 9 to 3 after 1 week of treatment with dupilumab that was accompanied by a significant reduction in levels of IL-31 in the patient's blood and skin.[84] At the same time, there was a transient increase in peripheral Sezary cell counts, which raises the concern of clinical worsening of the CTCL after treatment with dupixent, which has been reported in a previous case review.[85]

### 3.2 | Tralokinumab & lebrikizumab

A phase III clinical trial of tralokinumab, a monoclonal antibody against IL-13, for patients with moderate to severe AD found 20% of patients in the treatment group had at least a 4 point reduction in peak pruritus NRS compared to 10% in the placebo group after 16 weeks of treatment.[86] A recent phase IIb clinical trial of lebrikizumab, a monoclonal antibody with a high affinity for IL-13, was tested in patients with moderate to severe AD and found a 60% decrease in peak pruritus NRS from baseline in patients treated at a dose of 250 mg every 2 weeks, a 49% decrease for those treated with a dose of 250 mg every 4 weeks, a 35% decrease for those treated with a dose of 125 mg, and a 4% increase for those treated with placebo after 16 weeks of total treatment.[87]

### 3.3 | Nemolizumab & vixarelimab

A phase III clinical trial of nemolizumab, an anti-IL-31Ra monoclonal antibody, included 143 patients with moderate to severe AD and found a reduced peak pruritus VAS by an average of 42.8% from baseline compared to 16% by placebo after 16 weeks of treatment.[88] Furthermore, a phase III clinical trial of nemolizumab included 70 patients with moderate to severe PN found a significant reduction of peak pruritus NRS of 53% from baseline compared to 20% in the placebo group by week 4 of treatment.[89] A phase IIa clinical trial of vixarelimab, a monoclonal antibody against the OSMRb, included 49 patients with moderate to severe PN and found an average of 70% decrease of baseline peak pruritus NRS from baseline after 8 weeks of treatment.[90] The phase 2b trial is currently underway.[91]

### 3.4 | JAK/STAT inhibitors

The JAK–STAT signalling pathway is another important target of type 1–2 inflammation and indeed JAK–STAT inhibitors demonstrate robust anti pruritic effect. Phase III clinical trials of the oral JAK inhibitors abrocitinib, baricitinib and upadactinib have all demonstrated rapid improvement of peak pruritus NRS for patients with moderate to severe AD that was seen after 1 week of treatment and maintained throughout the 16 weeks of treatment.[92–94] In addition to AD, a case series of tofacitinib, an oral JAK inhibitor, has reported successful reduction of peak pruritus NRS for five elderly patients with CPUO that was refractory to other off-label therapies such as antihistamines, gabapentin, and topical steroids.[95] Treatment with topical ruxolitinib for patients with moderate to severe AD was shown to be efficacious after 8 h of treatment with an average decrease of 1.8 points in peak pruritus NRS from baseline.[96]

## 4 | CONCLUSION

As the role of type 2 immune response had been previously well-defined in itch secondary to atopic dermatitis, the breadth of targeted treatment options for itchy atopic patients has grown tremendously in recent years. Through the evidence we have presented in this article, we hope to have made a strong argument for similar roles of the type 2 immune response in chronic skin conditions beyond AD. We encourage future research investigating the specific involvement of the type 2 immune response in chronic pruritic conditions. In addition, this review highlighted therapeutic potential of drugs covering the Th2 immune response and effectively treat the itch in specific chronic skin conditions as well. In our opinion, the drugs that target the Th2 immune response may have a more robust effect on the primary outcome of disease resolution as well as the secondary outcome of disease-associated pruritus in diseases in which both the pathogenesis and pruritus are driven mainly by the Th2 immune response, such as AD, PN and BP. However, these medications may have limited efficacy in treating more effectively the diseases in which the pathogenesis and pruritus are driven by a multitude of molecules outside of the Th2 immune response, such as CSU, DM and CKD-aP. Although, we have previously shown that CTCL itch is driven by Th2 cytokines, the major concern is the long-term safety control of modulating cytokines such as IL-4, IL-13 or IL-31 on tumour biology or whether they have pro-tumour effects.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

All authors listed have contributed to the concept, design, analysis, writing and/or revision of the manuscript and have approved the final version of the paper. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. All individuals who meet authorship criteria are included as authors of this paper. All authors consent to the publication of this work.

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